REMARKS

Claims 1 to 12, as amended, appear in this application for the Examiner's review and consideration. The amendments are fully supported by the specification and claims as originally filed. Therefore, there is no issue of new matter.

Claims 1 to 12 were rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over U.S. Patent Application No. 2004/0181086 ("the '086 application"), apparently attributed to Javdani et al in the Office Action, An Experiment with Acid Water, a lesson plan created by John S. Cattaneo ("Cattaneo"), U.S. Patent 4,594,466 to Reeves, and Water Treatment: How Can We Make Our Water Safe To Drink?, by Kegley et al. ("Kegley").

Applicants note that the apparent attribution of the '086 application to Javdani et al. is incorrect. The inventors of the '086 application are Godbole et al. ("Godbole"). From the statement in the Office Action that "the US pregrant publication clearly teaches the crystallization of nitro-4-methlsulfonylbenzoic acid," Applicants believe that the correct reference to that process is U.S. Patent Application Publication No. 2004/0171872 to Javdani et al. ("Javdani").

In response to the rejection, Applicants respectfully submit that M.P.E.P. § 2141 states that, with regard to the basic considerations that apply to obviousness rejections,

> When applying 35 U.S.C. 103, the following tenets of patent law must be adhered to:
> (A) The claimed invention must be considered as a whole;
> (B) The references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination;
> (C) The references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention; and
> (D) Reasonable expectation of success is the standard with which obviousness is determined.

M.P.E.P. § 2143 further states

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

Applicants submit that, for the reasons set forth below, a *prima facie* case of obviousness has not been established in the Office Action. The cited references fail to disclose or suggest all of the limitations of the present claims, and the references, whether

taken alone or in combination, provide no motivation to one of ordinary skill in the art to modify any of the cited references to obtain the presently claimed invention. As the references do not disclose or suggest the presently claimed invention, or provide any motivation to obtain the presently claimed invention, the references do not provide the required reasonable expectation of success. Moreover, the Office Action does not consider either the presently claimed invention or each of the cited references as a whole. Instead, the Office Action simply points to specific elements of the invention, and alleges that those elements are found in the prior art. The rejection appears to be an impermissible hindsight reconstruction of the invention based on Applicants' disclosure. Thus, the rejections do not meet the requirements of M.P.E.P. §§ 2141 and 2143.

The presently claimed invention, as recited in claim 1, is directed to a process for purifying zoledronic acid, and, as recited in claim 12, is directed to the steps in a process for purifying zoledronic acid. The presently claimed process and the steps of the process comprise (a) raising the pH of an aqueous suspension of crude zoledronic acid until a clear solution is obtained; (b) lowering the pH of the solution obtained in (a) until zoledronic acid precipitates out of solution; and (c) isolating the zoledronic acid that has precipitated from the solution in (b). The presently claimed invention uses significantly less water, i.e., about half, than that required in prior art processes, which require recrystallizing the zoledronic acid from water at reflux temperature, as zoledronic acid is only sparingly soluble in water at room temperature. Present specification, pages 2 and 4. This is advantageous for ecological reasons and particularly for industrial applications.

To render the present claims obvious, one or more references, taken alone or in combination, must disclose or suggest all of the following claim elements:

Raising the pH of an aqueous suspension of zoledronic acid;

Producing a clear solution of zoledronic acid;

Lowering the pH of the resulting zoledronic acid solution;

Precipitating zoledronic acid from the solution; and

Isolating the zoledronic acid.

Each of the cited references fails to disclose or suggest anything regarding zoledronic acid generally. That is, none of the cited references refers to zoledronic acid or a related compound. Thus, each of the cited references fails to disclose or suggest purifying zoledronic acid with or without the presently claimed method. Moreover, none of the cited references discloses or suggests purifying any material by raising the pH of an aqueous suspension the material until a clear solution of the material is obtained, and lowering the pH

of the resulting solution until the material precipitates from the solution, as presently claimed for the purification of zoledronic acid. Therefore, none of the references, whether taken alone or in combination, disclose or suggest each and every one of the limitations of the present claims, as required by M.P.E.P. § 2143 for a *prima facie* case of obviousness. Moreover, as the cited references do not disclose or suggest anything regarding zoledronic acid, those references cannot provide any motivation to purify zoledronic acid or an expectation of success regarding the purification of zoledronic acid. Therefore, the cited references cannot be the basis for a *prima facie* case of obviousness.

In contrast to the presently claimed invention, Godbole discloses a process for the recovery of nitrite monomer from the reactor effluent of a ammoxidation of propylene, propane, isobutane, or isobutylene in the production of acrylonitrile or methacrylonitrite. Page 1, [0002]. Godbole discloses that the separation is greatly affected by pH, such that the pH must be maintained in the range from about 5.5 to about 7.5. Page 1, [0007]. In the disclosed process, the pH of the recovery column is maintained near neutral. Page 2, [0003].

Godbole does not disclose or suggest raising the pH of an aqueous suspension of crude zoledronic acid until a clear solution is obtained, and then lowering the pH of the solution until zoledronic acid precipitates out of solution. Instead, Godbole discloses maintaining the pH near neutral. Therefore, Godbole does not disclose or suggest the presently claimed invention.

Javdani discloses a method for removing impurities from NMSBA (2-nitro-4-methylsulfonylbenzoic acid). The disclosed method comprises at least two of the following steps, in any order: (a) dissolving NMSBA in water at a pH of about 2 to 10, followed by filtration; (b) contacting an aqueous solution of NMSBA with activated carbon at a pH of about 2 to 10; and (c) treating an aqueous solution of NMSBA with sufficient base to hydrolyze undesired nitro and dinitro substituted impurities. Paragraphs [0007] to [0010]. Those steps are followed by maintaining the temperature of the resulting aqueous NMSBA solution at about 95°C, and adjusting the pH of the solution to a pH that is sufficient to effect crystallization of NMSBA upon cooling. Paragraph [0011]. Javdani also discloses filtering the NMSBA solution, as such solutions are milky white mixtures even after caustic is added. Paragraphs [0024] and [0031].

Javdani does not disclose or suggest raising the pH of an aqueous suspension until a clear solution is obtained, and then lowering the pH of the resulting solution until precipitation occurs. Instead, Javdani discloses dissolving NMSBA in water at a pH of about 2 to 10, followed by filtration, treating the aqueous solution with sufficient base to hydrolyze

undesired nitro and dinitro substituted impurities, and adjusting the pH of the 95°C solution to a pH that is sufficient to effect crystallization of NMSBA upon cooling. This is not the presently claimed process, and, thus, Javdani does not disclose or suggest the presently claimed invention. Moreover, as dissolving a material in water at a pH of about 2 to 10 is not raising the pH of a suspension of the material until a clear solution is obtained, and adjusting the pH of a solution to a pH that is sufficient to effect precipitation upon cooling is not lowering the pH until precipitation occurs, Javdani fails to provide any motivation to obtain the presently claimed invention with a reasonable expectation of success. Therefore, Javdani does not disclose or suggest the presently claimed invention.

In addition, as Javdani teaches adjusting the pH and Godbole teaches maintaining a neutral pH, one of ordinary skill in the art would not combine the teachings of those references, and, thus, the implied combination of those references in the Office Action is improper.

Reeves does nothing to overcome the deficiencies of Godbole and Javdani. Reeves discloses a process for the recovery of weak organic acids, such as ethanol and methanol, from aqueous solutions of fermentation products for use as fuels. Column 1, lines 4 to 10 and 19 to 22. The disclosed process is directed at reducing the energy requirements in the production of ethanol, and involves altering the nature of the water component of the alcohol/water mixture produced by fermentation, such that the water and alcohol are no longer miscible, and phase separation occurs. Column 1, lines 43 to 59. As the alcohol/water mixtures are fermentation products, and alcohol is miscible in water at any pH, such that it forms a solution, not a suspension, Reeves does not disclose or suggest raising the pH of a suspension to obtain a clear solution, as presently claimed. Instead, the alcohol is produced in solution with water during fermentation. This is not a suspension of alcohol in water that is converted to a clear solution of alcohol in water by an increase in pH.

Reeves also discloses that the phase separation is accomplished by dissolving at least 26 g/100 ml of a base or basic salt, such as anhydrous potassium carbonate, which is more soluble in water than the alcohol in the alcohol/water mixture, resulting in the phase separation. Column 2, lines 14 to 25 and 36 to 41. Dissolving at least 26 g/100 ml of a base or basic salt in the alcohol/water mixture produces a solution substantially saturated with the base or basic salt, inducing the phase separation. Column 2, lines 46 to 49. Therefore, as will be understood by one of ordinary skill in the art, the phase separation results from the difference in the solubilities of the alcohol and base or salt in water, such that, when the saturated solution of base or salt is produced, the solubility of the alcohol in the solution is

decreased, and the base or salt replaces the alcohol in the solution. Accordingly, the phase separation does not occur as a result of a change in pH. The phase separation occurs as a result of the formation of a saturated solution of the base or salt that changes the solubility of the alcohol in water.

Moreover, as will be understood by one of ordinary skill in the art, the addition of a base or basic salt will raise the pH of the mixture disclosed by Reeves, and, thus, if any pH change occurs with the phase separation, it is an increase in pH, not the decrease in pH of the presently claimed invention. Reeves does not disclose or suggest lowering the pH of the alcohol/water mixture until precipitation occurs, and does not disclose of suggest the presently claimed invention.

Moreover, as Reeves discloses reducing the energy requirements in the production of a fuel, Reeves provides no motivation to one of ordinary skill in the art to first form a clear solution of the fuel with water in a process to purify it. If one of ordinary skill in the art had a suspension of the fuel in water, a phase separation would exist, and there would be no need to first dissolve the fuel, and then produce a phase separation to separate the fuel from the water.

As with the other references, Reeves fails to disclose anything regarding zoledronic acid, and fails to disclose or suggest purifying zoledronic acid by the presently claimed process.

Therefore, as Reeves does not disclose or suggest the presently claimed invention, and does not provide any motivation to obtain the presently claimed invention, the present claims are not obvious over Reeves. Moreover, Applicants submit that it is unclear how one of ordinary skill in the art would combine the teaching of Reeves with that of the other cited references.

Cattaneo fails to overcome the deficiencies of Godbole, Javdani, and Reeves. Cattaneo discloses a lesson plan that discloses that southwestern Pennsylvania mine water is a major source of pollution, and is the result of pyrite, FeS_2 oxidation. Cattaneo also discloses the standard definitions of acidity and pH, and the broad details of experiments in which a sample of acid mine water is duplicated, its effect on living plants is determined, and its acidity is neutralized.

That is, Cattaneo discloses classroom experiments that are intended to teach students about pollution and acidity, as well as how to at least partially purify polluted water. However, Cattaneo does not disclose or suggest anything regarding the purification of any material suspended or dissolved in the water, in particular, zoledronic acid, and, thus, does

not disclose or suggest the presently claimed invention, or provide any motivation to obtain the presently claimed invention.

In particular, Cattaneo discloses that a sample of acid mine water may be created by placing coal in a container, and covering the coal with water, such that, after a few days, the pH of the water decreases to 4 or less. Cattaneo then discloses an experiment that demonstrates that the pollutants in acid mine water can kill plants, and a second experiment that demonstrates that acid mine water may be "purified" by placing limestone in the acidic water. That is, the limestone reacts with and neutralizes the acid in the water. This may "purify" the water by neutralizing the acid in the water, but it does not purify anything that was originally suspended in the water.

Cattaneo does not disclose or suggest raising the pH of a suspension to form a clear solution of the suspended material, and then lowering the pH of the solution until the dissolved material precipitates, as is presently claimed for purifying zoledronic acid with the presently claimed process. Therefore, as Cattaneo does not disclose or suggest the presently claimed process, and does not provide any motivation to obtain the presently claimed process, the present claims are not obvious over Cattaneo.

Similarly, Kegley discloses what appear to be questions for a series of lesson plans that use water treatment to teach basic chemical principles, such as solubility, analytical methods for determining amounts of dissolved materials in water, equilibrium, Le Chatelier's principle, acids, bases, and pH. Kegley also provides animations of the dissolution of sodium chloride in water, the precipitation of copper ions with iodate ions, and two equilibrium simulators on the atomic scale.

As with the other references, Kegley fails to disclose anything regarding purifying zoledronic acid, as presently claimed, and fails to provide any motivation to one of ordinary skill in the art to purify zoledronic acid with the presently claimed invention. Kegley, does not disclose or suggest raising the pH of a suspension to form a clear solution of the suspended material, and then lowering the pH of the solution until the dissolved material precipitates, as is presently claimed for purifying zoledronic acid with the presently claimed process. Therefore, as Kegley does not disclose or suggest the presently claimed process, and does not provide any motivation to obtain the presently claimed process, the present claims are not obvious over Kegley.

One of ordinary skill in the art combining the teachings of Cattaneo and Kegley would obtain a series of lesson plans regarding water purity and acidity, but would not obtain the presently claimed invention. Moreover, combining the teaching of Cattaneo and Kegley

with that of the other cited references, would not provide the presently claimed invention, as none of the cited references disclose or suggest raising the pH of a suspension until a clear solution is obtained, and then lowering the pH of the solution until the material precipitates, as is presently claimed for zoledronic acid. The cited references, whether taken alone or in combination do not disclose or suggest the presently claimed invention, and fail to provide any motivation to obtain the presently claimed process for purifying zoledronic acid.

In addition, at page 3, the Office Action states: "the protein (amino acids) purification also teaches changing the pH to precipitate it out." However, the cited references, whether taken alone or in combination, do not disclose or suggest the purification of proteins or amino acids.

The Office Action, at page 3, also states: "Recrystallization techniques are an age old method which requires dissolving and then precipitating it out, but it is done by changing temperature."

In this regard, Applicants submit that the present specification, at page 4, lines 28 to 32 states:

> The inventive process is advantageous compared to a simple recrystallization of crude Zoledronic acid from water as the amount of water that is needed is significantly smaller (while a recrystallization process from water is performed at reflux temperature in order to achieve complete dissolution of the material in water). These two parameters may be even more significant when an industrial production is concerned.

Therefore, the present specification and the Office Action distinguish the presently claimed invention from a simple recrystallization.

At pages 3 and 4, the Office Action states that the prior art does not specifically teach "the techniques" with zoledronic acid, but does teach other acids, Le Chatelier's principle, and phase separations, such that one of ordinary skill in the art would allegedly have found it obvious to purify by varying the pH. However, none of the cited references disclose or suggest the "techniques" of the presently claimed invention.

That is, the disclosed references do not disclose or suggest purifying a compound with the steps of dissolving and precipitating the compound by raising the pH of a suspension of the compound to provide a clear solution of the compound, and lowering the pH to precipitate the compound, as presently claimed for purifying zoledronic acid.

As discussed above, Javdani discloses removing impurities from NMSBA by at least two of the steps of filtration, contact with activated carbon, and hydrolysis of nitro and dinitro

substituted impurities, and does not disclose or suggest obtaining a clear solution before lowering the pH. Instead, Javdani discloses dissolving a material in water at a specific pH, forming a milky mixture that must be filtered.

Reeves discloses separating ethanol from an aqueous fermentation mixture by adding a base or basic salt to the mixture that is more soluble in water than the alcohol to form a saturated solution of the base or basic salt, which changes the miscibility of the alcohol and water, resulting in a phase separation. The phase separation is not the result of a change in pH, and, if any change in pH occurs with the phase separation, it is an increase in pH, not the decrease in pH that results in the precipitation of zoledronic acid in the presently claimed invention.

Godbole teaches maintaining a constant pH, not changing the pH as presently claimed.

Cattaneo and Kegley are directed to the purification of the solvent, not the solute, and do not disclose or suggest raising the pH of a suspension to form a clear solution, and then lowering the pH such that a precipitation occurs.

None of the cited references, whether taken alone or in combination, provide any motivation to one of ordinary skill in the art to purify zoledronic acid using the method of the invention with a reasonable expectation of success. First there is no disclosure or suggestion in any of the cited references regarding zoledronic acid or the purification of zoledronic acid. In addition, the chemical and physical properties and the impurities of all of the constituents of the mixtures and compositions disclosed in the cited references are substantially different from those of zoledronic acid and suspensions and solutions of zoledronic acid and the impurities in the zoledronic acid and the zoledronic acid suspensions and solutions.

For example the alcohol disclosed by Reeves, the NMSBA disclosed by Jadvani, and the acids disclosed by Cattaneo and Kegley are all highly miscible with water, while zoledronic acid is not. In addition, the impurities removed from zoledronic acid in the method of the invention would be understood by one of ordinary skill in the art to be different from those of the cited prior art references. For example, two of the impurities of zoledronic acid are identified at page 3 of the present specifications as imidazole and IAA (i-imdazoleacitic acid). The cited references do not disclose or suggest such impurities or any means to remove such impurities.

Finally, the Office Action states

> The state of the art is such that one would have found it obvious to purify by varying the pH. Water treatment plant use the same principal

on a large scale to remove impurities. And also separation of acids is taught by the prior art.

Thus one of skill in the art would have found it obvious to purify zoledronic acid by increasing and then lowering the pH.

However, as discussed above with regard to the cited references, the Office Action has not provided any reference that discloses or suggests raising the pH of a suspension until a clear solution is obtained, and then lowering the pH of the solution until precipitation occurs, as presently claimed for zoledronic acid.

Therefore, as Javdani, Reeves, Godbole, Cattaneo and Kegley, whether taken alone or in combination do not disclose or suggest the presently claimed invention, and fail to provide any motivation to one of ordinary skill in the art to purify zoledronic acid with a reasonable expectation of success using the presently claimed invention, the present claims are not obvious. Accordingly, it is respectfully requested that the Examiner withdraw the rejection of claims 1 to 12 under 35 U.S.C. §103(a).

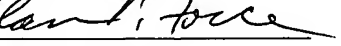
Applicants thus submit that the entire application is now in condition for allowance, an early notice of which would be appreciated. Should the Examiner not agree with Applicants' position, a personal or telephonic interview is respectfully requested to discuss any remaining issues prior to the issuance of a further Office Action, and to expedite the allowance of the application.

The Extension-of-Time Fee due for the submission of this Amendment is believed to be $1,020.00. A separate Amendment Transmittal authorizing the payment of the fee is submitted herewith. Should any other fee be due, please charge such fee to Deposit Account No. **11-0600**.

Respectfully submitted,

KENYON & KENYON

Dated: August 11, 2005

By: 

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